IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Beka SOLOMON

Application No. 09/441,140
Filed: November 16, 1999

PREVENTION OF PROTEIN AGGREGATION

Examiner: K. Ballard
Art Unit: 1649

REPLY BRIEF

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Attorney Docket: SOLOMON=1R

Date: May 31, 2011

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The present reply brief is responsive to the examiner's answer of March 30, 2011, and is in full accordance with 37 C.F.R. 41.41.

The Examiner's Responses Regarding the New Matter Rejection Do Not Establish Lack of Support for the Claim Language

At page 24 of the Examiner's Answer, the examiner states that the aggregation assay disclosed in example 2 and shown in Figures 7A and 7B was used to test whether the AMY-33 or 6F/3D antibodies could individually affect the aggregation of β-amyloid under different aggregating conditions, rather than explicitly to compare the antibodies' anti-aggregating properties to each other. In response, those of ordinary skill in the art reading the present specification would clearly understand that any given antibody could be tested for its anti-aggregating properties by means of this assay. Furthermore, whether or not the assays occur side by side (and the tests of Figs. 7A and 7B were conducted side by side (col. 13, lines 30-32), still the results are quantitative and it can readily be determined whether the results are poor, as demonstrated for 6F/3D, or whether the results are as good as or better than those obtained with AMY-33. A disclosure includes not only what is explicitly disclosed but also what is implicitly or inherently disclosed.

The examiner states that *In re Wertheim,* 541 F.2d 257, 191 USPQ 90 (CCPA 1976), does not support applicant's position that the claimed feature of being at least as good as AMY-33 is supported by the written description of the specification. The examiner refers to the example of *Wertheim* in which it was found that "at least 35%" did not meet the description requirement because it caused the claim to read literally on embodiments outside the "25% to 60% range. However, that is not the case in the present application. The present claim range, i.e., being at least as good as AMY-33, does not read literally on embodiments outside the widest range specifically disclosed, i.e., having any activity from minimal to the maximum possible. Thus, the example of *Wertheim* relied on by the examiner is inapplicable to the present situation.

The examiner states that the recitation of "at least as" implies a functional activity that includes those antibodies with equivalent or greater functional activities than that of AMY-33, but the specification provides only one antibody with the exact activity of AMY-33. The examiner states that the specification as originally filed therefore did not explicitly or implicitly indicate this subgenus of antibodies as part of the invention.

In response, it must first of all be pointed out that applicant disagrees with the examiner's characterization of the degree of aggregation inhibition activity being a "functional activity." The ability to inhibit aggregation is a **property** of the antibody. The "at least as" is a quantification of that property. The specification supports antibodies with all activities from a very small amount to the maximum possible. AMY-33 provides proof of concept, but those of ordinary skill in the art understand that other antibodies may be found that have such activity and they would not be expected to have the exact same activity of AMY-33. It would be expected that some would have more activity and some less. The genus of all of those antibodies is included in the present specification and is supported by the example of AMY-33. Similarly, the subgenus of only those having the activity equal to AMY-33 or more is also supported by the single embodiment of AMY-33 which provides a proof of concept. In any event, it is not understood how this argument of the examiner supports a new matter rejection.

The examiner states that not all antibodies that recognize an epitope within residues 1-28 of β-amyloid are capable of inhibiting aggregation of β-amyloid and or maintaining the solubility of soluble β-amyloid, as can be

seen by the TABLE of record. Thus, the examiner states that, based on the art-recognized unpredictability and the limited disclosure of only one antibody, the skilled artisan would not recognize that appellant reasonably provided an adequate written description of a subgenus of antibodies that meet or exceed the functional activity of the AMY-33 antibody. In response, the entire genus of antibodies (without the at least as great as AMY-33 limitation) has the same issue of unpredictability. This is discussed in the section below relating to the written description rejection. The issue of predictability thus really has nothing to do with the new matter rejection. While it cannot be predicted whether any given antibody will inhibit aggregation at all, or, if so, will inhibit to an extent at least as great as AMY-33, it is fully predictable that there will be such antibodies among the hybridomas obtained in any batch raised against Aβ1-28 as an immunogen.

The Claimed Genus of Antibodies is Adequately Supported by the Written Description

The examiner states that to provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The examiner states that in the present claims, the

only factors present are a recitation of the desired inhibitory functional property, a generic binding recitation, and the immunogenic peptide fragment used to obtain the monoclonal antibody from which the claimed genetically engineered antibody is derived. The examiner states that these do not serve to limit the antibody structure. The examiner states that there is no indication of particular structural or physical properties of the claimed antibodies or of any structure/function correlation for antibodies capable of inhibiting β-amyloid aggregation. The examiner cites *University of Rochester v. G.D. Searle & Co., Inc.*, 558 F3d 316 (Fed. Cir. 2004), for the notion that possession may not be shown by merely describing how to obtain possession of members of the claimed genus. The examiner states that there is no description in the instant application nor commonly available in the prior art to sufficiently correlate the desired function – that of inhibiting aggregation of β-amyloid, maintaining the solubility of soluble β-amyloid or recognizing an epitope within residues 1-28 of β-amyloid – with that of a particular known structure. Therefore, the examiner concludes that conception is not achieved until reduction to practice has occurred and regardless of the complexity of simplicity of the method of selection, isolation

and/or production, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The examiner states that the compound itself is required. These conclusions are respectfully traversed.

The present specification includes a general discussion of how to make monoclonal antibodies using a specific peptide, such as Aβ1-28, as the immunogen. See column 11, at the section beginning at line 32. Those hybridomas are selected that secrete the required antibody (column 11, lines 48-49). At the top of column 12, the specification goes on to state that commercially available antibodies may alternatively be used for antibodies raised in the manner described. For the sake of convenience, such available antibodies were used in the further experiments in the present specification. However, it is very clear from this section of the specification that the present inventor was fully in possession of the conception of raising monoclonal antibodies in the standard manner and using those that bind to the immunogen in the same assays in which the commercial antibodies were used in the remainder of the specification. The amyloid ELISA assay was described beginning at column 13, line 19, and Example 2 details the

results of these assays. At column 16, lines 15-21, the present specification clearly states that the invention provides a general and convenient method to prevent aggregation of the proteins.

The state of the law of written description was recently detailed by the *in banc* Federal Circuit in *Ariad v. Eli Lilly,* 598 F3d 1336, 94 USPQ 2d 1161 (Fed Cir 2010). In speaking of written description support for generic claims, *Ariad* states that 1349:

> But the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to this functionally defined genus.

Ariad further states at 1350:

> [A] sufficient description of a genus … requires the disclosure of either a representative number species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can "visualize or recognize" the members of the genus. … [A]n adequate written description requires a precise definition, such as by … physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials.

Ariad at 1351 states:

> For generic claims, we have set forth a number of factors for evaluating the adequacy of the disclosure, including "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue." [Citing *Capon v. Eshhar*, 418 F3d 1349, 1359 (Fed. Cir. 2005).]

Furthermore, *Ariad* at 1352 states:

> We have made clear that the written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement.

In discussing the *Rochester* case, *supra*, *Ariad* states at 1353:

> We reasoned that because the specification did not describe any specific compound capable of performing the claimed method and the skilled artisan would not be able to identify any such compound based on the specification's function description, the specification did not provide an adequate written description of the claimed invention.

In view of this discussion of the treatment of the written description requirement in *Ariad*, it is clear that the examiner's reliance on the *Rochester* case is misplaced because the present specification (in contrast to the *Rochester* situation) does describe at least one specific compound having the claimed properties. Thus, the holding in *Rochester* is inapplicable here.

The present claims do not recite the antibodies merely by means of a functional statement but rather recite specific properties that the antibodies possess. These properties include binding to β-amyloid and either inhibiting aggregation of soluble β-amyloid or causing disaggregation of aggregated β-amyloid. Thus, this definition of the antibody is a "precise definition, … by physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials." This is considered to be sufficient based on the above quoted language from *Ariad*. There is no *per se* requirement that the product be described by structure or formula. Other means of description are permitted.

Furthermore, the present specification discloses a species within the genus which is sufficient to support the genus in view of the fact that it is such a simple matter to find other species within the genus. While the examiner states that the simplicity or complexity is irrelevant, *Ariad* specifically states that the level of detail required to satisfy the written description requirement varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology. The described assay is simple to carry out and, because of the existence of

the disclosed antibody AMY-33, it is highly predictable that other antibodies with the required properties will be found in this manner.

The *Capon* factors for evaluating adequacy of written description, as listed in *Ariad,* include (1) the existing knowledge in the particular field, (2) the extent and content of the prior art, (3) the maturity of the science or technology, and (4) the predictability of the aspect at issue. Here, the existing knowledge in the field is very high, the prior art is extensive and the monoclonal antibody technology is very mature. See, for example, *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002). Similarly, not only the generation of antibodies, but also the selection of those antibodies with the enumerated specific properties by appropriate assays is well known in the existing art. Thus, the antibody art is full and mature. As to the predictability of the aspect at issue, while it is true that it cannot be predicted whether any given antibody raised against the Aβ1-28 peptide will necessarily have the required properties, it is fully predictable that a certain percentage of all those antibodies obtained will, and these can be simply and readily "filtered out" by means of the fully described assay. Thus,

the *Capon* factors warrant a conclusion of adequacy of the disclosure.

As far as meeting or exceeding the quantitive capability of AMY-33, again, this a property that would be readily apparent from the assay conducted of those antibodies that bind β-amyloid. It is noted that the examiner concedes that the written description is complete for all monoclonal antibodies that bind β-amyloid. Side by side tests with AMY-33 are not necessary as figures 7A and 7B of the present specification show quantitative results for AMY-33, and the results for any other antibody can readily be compared in the same assay.

Two non-precedential Board decisions are of interest with respect to this issue. One is *Ex parte Xia*, Appeal No. 2008-3329, Application 10/242,092 (Bd Pat App & Int, January 28, 2009). A copy of this opinion, as obtained from the USPTO website, is attached hereto. The representative antibody claim reads:

> 21. A rabbit monoclonal antibody having a specific affinity for human progesterone receptor that is higher than that of murine monoclonal antibody 1A6, wherein the rabbit monoclonal antibody specifically binds an epitope within amino acids 412-562 of the progesterone receptor B form present in ….

The examiner made a written description rejection based on the fact that the specification taught only a single species of undefined structure and properties binding to an unknown and unpredictable epitope in a 151 amino acid sequence. The Board reversed, stating at slip opinion page 8:

> All that is required, however, for adequate written description of an antibody is the disclosure of a fully characterized antigen, which requirement is met by the Specification …. We decline to read into that requirement that the Specification also disclose the specific epitope bound by the antibody, or the structure of the antibody.

By the standard of the *Xia* case, which comports with the law of the Federal Circuit, the present claims must also be free of any written description objection. As in *Xia*, the present claims recite a property that is determined in relationship to another antibody. As in *Xia*, the present claims specify the fully characterized antigen used to obtain the antibodies. Thus, just as the claim in *Xia* was found to be supported by an adequate written description, so must be the present claims.

Another non-precedential opinion that is of interest is *Ex parte Gleave*, 84 USPQ2d 1681 (Bd Pat App & Int 2006), copy attached. In that case, claim 1 read:

> 1. A method for delaying progression of hormone-regulated mammalian tumor cells to an androgen-independent state, comprising

> treating hormone-sensitive mammalian tumor cells with an antisense oligonucleotide which inhibits expression of IGFBP-5 by the tumor cells.

The examiner argued that the specification only described two target IGFBP-5 sequences, mouse and human, and did not describe any additional sequences that can be targeted via antisense oligos. Without such a description, the skilled artisan would not be able to envision any other target sequences and thus would not be able to synthesize an antisense oligo specific for the sequence and would be required to undertake *de novo* experimentation to isolate and identify IGFBP-5 encoding nucleic acids.

The Board reversed this rejection, saying that the specification sets forth the sequences of DNA molecules encoding the mouse and human IGFBP-5's, as well as a number of antisense sequences targeting specific regions of the mouse and human IGFBP-5 DNAs. The Board pointed out that the examiner's rationale would seem to limit the claimed genus to only those antisense oligonucleotides explicitly recited, without explaining why one skilled in the art would not have expected the mouse and human DNAs to be representative of, or have considerable structural similarity to, DNA encoding IGFBP-5 in other mammals.

On the other hand, claim 8 called broadly for the use of a composition effective to inhibit expression of IGFBP-5 by the hormone-responsive cancer cells. The Board affirmed the written description rejection with respect to claim 8, wherein the examiner's position was essentially that the specification does not provide any description, structural or otherwise, of IGFBP-5 inhibitors other than the instantly described antisense oligonucleotides and that the instantly described antisense oligonucleotides are not representative of the breadth of inhibitors sought in the instant claims. The Board affirmed this rejection and held that such claims were impermissible under *Rochester* as the claims are directed to a process for accomplishing a desired result using a composition having a specified functional property. The Board explained that the genus recited in the claims is defined exclusively in functional terms, i.e., in terms of what the members of the genus do, rather than what they are.

The present claims are much more like claim 1 of *Gleave* than claim 8. They do not claim anything that has a certain function. They claim antibodies that have certain properties and are raised using a fully characterized antigen. The present antibody claims should not be considered

functional for the same reasons that the antisense molecule as defined in *Gleave* claim 1 was not considered functional.

For all of these reasons, the present inventor was clearly in possession of the full scope of the present claims, i.e., antibodies which have the property of inhibiting aggregation or causing disaggregation of β-amyloid. Given that, the inventor was also indisputably in possession of the genetically engineered forms of such antibodies. Accordingly, reversal of the examiner and withdrawal of this rejection are respectfully urged.

Even if a *Prima Facie* Case of Obviousness has been Established, the Evidence of Record Rebuts Any Such Case of *Prima Facie* Obviousness and Establishes the Patentability of the Present Composition Claims.

While applicant does not believe that the examiner has established a *prima facie* case of obviousness, for the reasons of record, the present discussion is applicable even if the Board agrees with the examiner that a *prima facie* case of obviousness has been established. As stated by the *in banc* court of *In re Dillon*, 919 F.2d 688, 692-693 (Fed. Cir. 1990):

> This court, in reconsidering this case *in banc*, reaffirms that structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness, and that the burden (and opportunity) then falls on an applicant to

> rebut that *prima facie* case. [Emphasis added]

As in *Dillon*, the examiner here claims to have established the *prima facie* obviousness of genetically engineered AMY33 or 10D5 antibodies. The examiner states that the unmodified antibodies of the prior art share in common with the genetically engineered antibodies of the present invention, the property of binding to β-amyloid plaque, useful in a diagnostic utility or in an immunotherapeutic utility in which an active therapeutic molecule is linked to the antibody, where the antibody is merely used to home the therapeutic molecule to the aggregated β-amyloid. However, as indicated from the above quote of *Dillon*, applicant has the opportunity to provide evidence of unexpected results to rebut the *prima facia* case. Here, the record shows that applicant has indeed established such unexpected results.

In *Dillon*, the examiner's rejection was affirmed, the court holding that a *prima facie* case of obviousness had been established, but the rebuttal evidence of record was insufficient to overcome it. Note where the *in banc* Federal Circuit stated in *Dillon*, at 694:

> However, after the PTO made a showing that the prior art compositions suggested the claimed compositions, the burden was on the applicant to overcome the presumption of obviousness that was created, and that was

> not done. For example, she produced no evidence that her compositions possessed properties not possessed by the prior art compositions. Nor did she show that the prior art compositions and use were so lacking in significance that there was no motivation for others to make obvious variants. **There was no attempt to argue the relative importance of the claimed compositions compared with the prior art. See *In re May*, 574 F.2d 1082, 1092-95, 197 USPQ 601, 609-11 (CCPA 1978).** [Emphasis added]

The present case differs from *Dillon* in that the record establishes rebuttal of any *prima facie* case of obviousness. It is very clear from a reading of the present specification that the present invention is based on the discovery that the "naked" antibody (without a linked drug) has therapeutic properties: reduction of the amyloid plaque and inhibition of the aggregation of soluble β-amyloid. Clearly, therefore, if one were to combine the references as suggested by the examiner to produce a genetically engineered antibody for use as a diagnostic alone (based on the expected property of binding to β-amyloid) or as an immunotherapeutic when conjugated to a therapeutic molecule (based on the expected property of the antibody homing to β-amyloid), one would not only achieve the expected binding or the expected therapeutic effect (of the therapeutic molecule bound to such an antibody), but **one would unexpectedly achieve the unknown**

and surprising therapeutic activity of the antibody itself without any linked therapeutic molecule. This unexpected reduction of plaque and/or inhibition of β-amyloid aggregation of the "naked" antibody, when the only reasonable expectation was the binding or homing of the antibody, would have been **totally surprising** at the time the present invention was made.

Evidence of these unexpected results of the present invention may be found in many publications in the prosecution record of this case. On September 23, 2009, a TABLE was submitted that summarized the results reported in the literature as to the availability of various antibodies against β-amyloid that could prevent aggregation of soluble β-amyloid or disaggregate aggregated β-amyloid. A copy of this TABLE was attached to Appellant's Main Brief on appeal. One of the antibodies in the TABLE was AMY-33, the very antibody used by Bickel and which the examiner concedes has the properties required of the antibody used to make the present genetically engineered antibody. The Hanan (1996) and the Solomon (1996) publications of record prove that this antibody prevents β-amyloid aggregation *in vitro*. See also the experimental evidence in the present specification. This property of AMY33 was **not known** as of the effective filing date of the present application.

The same applies for antibody 10D5, the very antibody used by Walker and which the examiner concedes has the properties required of the antibody used to make the genetically engineered antibody of the present claims. The Bacskai (2001) publication and the Bard (2000) publication, both of record, prove that this antibody causes disaggregation of aggregated β-amyloid *in vivo*. The Bard (2003) publication and the Schenk patent (US 6,761,888), both of record, establish that 10D5 causes disaggregation of aggregated β-amyloid *in vitro* or *ex vivo*. None of the secondary references cited by the examiner create an expectation that either of these antibodies will have these very important therapeutic properties.

Nobody reading Bickel or Walker would expect that the genetically engineered antibody (naked) or the genetically engineered antibody/therapeutic molecule conjugate that the examiner considers to be *prima facie* obvious would be able to disaggregate aggregated β-amyloid and/or inhibit aggregation of soluble β-amyloid. Thus, there is highly surprising physical evidence of record of the properties of the genetically engineered AMY-33 or 10D5 antibodies that the examiner considers obvious.

All of the publications establishing the results with AMY-33 and 10D5 are post-filing date publications, many from the laboratory of the present inventor. None are available as prior art. As the properties that give these antibodies their utility as proved in the publications discussed above are part of the definition in the present claims, the showing of unexpected results is commensurate in scope with the claims. The AMY-33 and 10D5 antibodies are representative of the genus of antibodies defined in the claims. Besides, the TABLE shows many other antibodies with the same properties, namely, 6C6, 3D6, 12B4, 2C1, 12A11, 3A3, and 22C8. If any of these antibodies were genetically engineered and substituted for genetically engineered AMY-33 or 10D5, allegedly "suggested" by the prior art, one would always get an antibody with unexpected properties for the reasons discussed above for AMY-33 and 10D5. All would cause disaggregation and/or inhibition of aggregation that would be above and beyond any β-amyloid binding effect expected from the prior art and would have been unexpected and surprising to anyone of ordinary skill in the art at the time the present invention was made.

It should be understood that applicant is not contending that the genetically engineered antibodies of the

present invention have properties that are not possessed by the antibody prior to its being genetically engineered. Indeed, the present claims specify that the genetically engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that (i) binds β-amyloid and inhibits aggregation of β-amyloid or maintains the solubility of soluble β-amyloid to an extent at least as great as that obtainable with antibody AMY-33 (e.g., claim 210) or (ii) binds β-amyloid and disaggregates an aggregate of β-amyloid (e.g., claim 219). However, the results for the presently claimed genetically engineered antibodies are nonetheless unexpected and thereby rebut any *prima facie* case of obviousness, because the prior art was unaware that the known antibodies had these properties.

As indicated in the above quoted portion of the *in banc Dillon* decision, the Federal Circuit recognized that a *prima facie* case of obviousness may be rebutted by arguing the relative importance of the claimed compositions compared with the prior art, citing *In re May*. In the *May* case,

> … appellants' evidence establishes that a single prior art homologue (disclosed in May) of the claimed compound … inherently possessed, unbeknownst to the prior art, the combination of properties of appellants' compound.

574 F.2d at 1094. This was still considered to be an unexpected property. The *May* court explicitly stated that if both unexpected properties and structural obviousness exist, then "those properties which would have been expected must be balanced against the unexpected properties." 574 F2d at 1094. The invention in *May* involved an analgesic or pain relieving drug. The inventors discovered that their new class of compounds, in addition to possessing the expected property of analgesia, also possessed the unexpected property of non-addictiveness. In making the ultimate determination on the issue of obviousness, the *May* court determined that the unexpected property of non-addictiveness was clearly overall more significant than the expected property of analgesia in the claimed analgesic compound. The *May* court held that this was true not only for method of use claims but also for composition claims, because the properties of a composition are part of the invention as a whole. *May* concluded, 574 F2d at 1095:

> Balancing the *prima facie* case of obviousness made out by the PTO against appellants' objective evidence of nonobviousness, we hold that the subject matter of [composition] claims 11-13 would not have been obvious to one of ordinary skill in the art.

Here, the therapeutic property of the monoclonal antibody, which was unknown in the prior art, is far more significant (in analogy to *May*) than the common property of merely binding to β-amyloid. Binding to β-amyloid is of interest in diagnostics as it allows imaging of the brain regions having amyloid plague or as an immunotherapeutic to direct a conjugated therapeutic molecule to the plaque. But the newly discovered fact that the naked antibody can inhibit aggregation of soluble β-amyloid and/or cause disaggregation of aggregated β-amyloid confers on the antibody a "direct" therapeutic capacity which is far more significant than the mere diagnostic (binding) property or the mere ability to carry some other drug. Indeed, when used as a carrier for another drug, the net therapeutic effect will be of both the antibody and the conjugated drug. Accordingly, as in *May*, balancing the Office's *prima facie* case of obviousness against the objective evidence of non-obviousness of record, one must conclude that the subject matter of the present claims would not have been obvious to one of ordinary skill in the art.

CONCLUSION

For all of the reasons presented herein, in conjunction with the reasons explained in appellant's main

brief, reversal of the examiner and withdrawal of all of the rejections of record are earnestly solicited.

Respectfully submitted,

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte HAIYING XIA and ZHIDA HUANG

Appeal 2008-3329
Application 10/242,092
Technology Center 1600

Decided: January 28, 2009

Before DEMETRA J. MILLS, LORA M.GREEN, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 21-27, 29, and 30. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

The claims are directed to a rabbit monoclonal antibody having specific affinity for the human progesterone receptor, as well as a method for selecting a monoclonal antibody that is suitable for immunohistochemical analysis of human progesterone receptor. Claims 21 and 25 are representative of the claims on appeal, and read as follows:

21. A rabbit monoclonal antibody having a specific affinity for human progesterone receptor that is higher than that of murine monoclonal antibody lA6, wherein the rabbit monoclonal antibody specifically binds an epitope within amino acids 412-562 of the progesterone receptor B form present in a fresh tissue section and present, in the absence of a tissue section processing step involving proteolytic digestion or heat treatment for antigen retrieval, in a formalin-fixed, paraffin-embedded tissue section after processing steps of deparaffinization and rehydration.

25. A method for selecting a monoclonal antibody for immunohistochemistry analysis of a human progesterone receptor, said method comprising the steps of:

a) contacting a rabbit monoclonal antibody of a plurality of rabbit monoclonal antibodies with a formalin-fixed, paraffin-embedded tissue section that contains the progesterone receptor, in the absence of a tissue section processing step involving proteolytic digestion or heat treatment for antigen retrieval, and after processing steps of deparaffinization and rehydration; and

b) detecting specific binding of the monoclonal antibody to the progesterone receptor in the absence of antigen retrieval to select the monoclonal antibody from the plurality of monoclonal antibodies for immunohistochemistry analysis of the progesterone receptor.

The Examiner relies on the following evidence:

Press et al. "Comparison of different antibodies for detection of progesterone receptor in breast center," 67 Steroids 799-813 (2002).

We reverse.

ISSUE (Written Description)

The Examiner finds that claims 21-27, 29, and 30 fail to comply with the written description requirement of 35 U.S.C. § 112, first paragraph.

Appellants contend that the claimed antibody was described as to the antigen used, *i.e.*, the PR B 412-562 antigen, which was recombinantly produced, and thus the claims are compliance with the written description rejection.

Thus, the issue on Appeal is: Is the description of the antigen used to produce the claimed antibody, *i.e.*, the PR B 412-562 antigen, which was recombinantly produced, sufficient to meet the written description requirement of 35 U.S.C. § 112, first paragraph, of the claims to the antibody?

FINDINGS OF FACT

FF1 The Specification teaches that "the assessment of estrogen and progesterone receptors (ER and PR) status in breast cancer is widely used for the prediction of response to endocrine therapy and as a prognostic marker." (Spec. 2.)

FF2 Immunohistochemical methods, in which ER and PR antibodies are used to test for the receptors on formalin-fixed, paraffin-embedded tissues, are considered to be a specific, sensitive, and economical method for determining receptor status (*id.*). One drawback of the immunohistochemical methods, however, is that it requires heat pretreatment of the sample, required for target retrieval, to be accurate (*id.* at

3). The Specification thus notes that it would be desirable to have a test system that does not require the heat pretreatment (*id.*).

FF3 The Specification thus discloses high affinity rabbit monoclonal antibodies for ER (clone SP1) and PR (clone SP2) (*id.* at 4).

FF4 According to the Specification, "general[ly], it has been found that a rabbit monoclonal antibody has higher affinity than a mouse monoclonal antibody," thus "it was hypothesized that rabbit monoclonal antibodies would be effective for immunohistochemistry testing." (*Id.* at 7.)

FF5 For the antigen,

> the PR gene encoding human PR B Form 412-562 aa was amplified by polymerase chain reaction (PCR) from human uterus PCR ready cDNA. The PR gene was then ligated into an expression plasmid. The presence of the PR gene in the plasmid was verified by DNA sequencing and the expressed PR 412-562 aa recombinant protein in E. Coli was confirmed by the protein size on the Commasie blue stained SDS-polyacrylamide gel and western blotting. The affinity purified recombinant protein was used as immunogen.

(*Id.* at 10-11.)

FF6 Positive clones were tested for tissue staining screen and the two best clones were selected "which gave strong signal and very low background in tissue staining without heat pretreatment." (*Id.* at 18.) The clone that produced the antibody with the strongest staining was named clone SP2 (*id.*).

FF7 The Examiner rejects claims 21-27, 29, and 30 under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (Ans. 3.)

FF8 The Examiner finds that the Specification "does not provide sufficient recitation of distinguishing identifying characteristics of the genus of antibodies, or even for the single disclosed functional species of SP2 antibody." (*Id.* at 4.)

FF9 According to the Examiner, the Specification "provides no guidance as to what modifications or structure are important for the predictable function of [SP2] or any other monospecific antibody." (*Id.*)

FF10 The Examiner finds further that the Specification "does not identify the epitope bound by the SP2 antibody and only localizes binding to the sequence comprising amino acid residues 412-562 of the human progesterone receptor B isoform." (*Id.* at 5.)

FF11 The Examiner notes that "[a] sequence of 151 amino acid residues, having numerous differences (about 38 mismatches) between the human sequence and the corresponding sequence in rabbits, has many potential unpredictable immunogenic epitopes therein which could be recognized as foreign in rabbits." (*Id.*)

FF12 The Examiner finds that "[g]iven the lack of guidance to the relevant epitope and unpredictability of the relevant structures of the epitopes and of the fine specificities of the antibodies elicited in a rabbit, even of the SP2 antibody, one would not know or be able to predict or envision what epitopic fragments were important for function." (*Id.*) Thus, the Examiner finds that the "description has not provided any guidance for a structure/function correlation identifying the genus because one does not know and cannot

envision the structure of the antibody or the epitope to be bound thereby." (*Id.* at 5-6.)

FF13 Citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991), the Examiner finds that "the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of antibodies and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation." (Ans. 6.)

FF14 The Examiner thus finds:

> However, as set forth above, appellant only teaches a single species of undefined structure and properties. Here, a single species of undefined structure and properties is not found to describe a genus of molecules, a genus with unknown structures and properties other than that they share the property of binding to unknown and unpredictable formalin-resistant epitope(s) in a 151 amino acid sequence.
>
> Therefore, only the SP2 antibody, if provided via a deposit in compliance with the Deposit rules, but not the full breadth of the claims, has the potential to meet the written description provision of 35 U.S.C. $1 12, first paragraph.

(*Id.* at 6-7.)

PRINCIPLES OF LAW

"The burden of showing that the claimed invention is not described in the application rests on the PTO in the first instance." *In re Edwards*, 568 F.2d 1349, 1354 (CCPA 1978). To comply with the written description requirement, the Specification must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, [the inventor] was in

possession *of the invention.*" *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). "[T]he determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter." *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005).

For antibody claims, which are defined by their function rather than the structure of the antibody *per se*, the Court of Appeals for the Federal Circuit, our reviewing court, has adopted the USPTO Written Description Guidelines

> as persuasive authority for the proposition that a claim directed to "any antibody which is capable of binding to antigen X" would have sufficient support in a written description that disclosed "*fully characterized* antigens." Synopsis of Application of Written Description Guidelines, at 60, *available at* http://www.uspto.gov.web.menu.written.pdf (last visited Jan. 16, 2003) (emphasis added).

Noelle v. Lederman, 353 F.3d 1343, 1349 (Fed. Cir. 2004); *see also Enzo Biochem Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964 (Fed. Cir. 2002). Therefore, "as long as an applicant has disclosed a 'fully characterized antigen,' either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding to that described antigen." *Noelle*, 355 F.3d at 1349.

ANALYSIS

Appellants argue that the claimed antibody was described as to the antigen used, *i.e.*, the PR 412-562 antigen, which was recombinantly produced, and thus the claims are compliance with the written description rejection (App. Br. 3).

We agree. The Specification describes a "rabbit monoclonal antibody having a specific affinity for human progesterone receptor that is higher than that of murine monoclonal antibody lA6, wherein the rabbit monoclonal antibody specifically binds an epitope within amino acids 412-562 of the progesterone receptor B form present in a fresh tissue section and present, in the absence of a tissue section processing step involving proteolytic digestion or heat treatment for antigen retrieval, in a formalin-fixed, paraffin-embedded tissue section after processing steps of deparaffinization and rehydration," that is, antibody SP1, and also describes the immunogen that was used to produce the antibody (FF5).

The Examiner appears to be requiring that the Specification disclose both the specific epitope recognized by the antibody (*see, e.g.*, FF10), as well as the structure of the antibody (*see, e.g.*, FF9). All that is required, however, for adequate written description of an antibody is the disclosure of a fully characterized antigen, which requirement is met by the Specification (FF5). We decline to read into that requirement that the Specification also disclose the specific epitope bound by the antibody, or the structure of the antibody.

To the extent that the Examiner is concerned about the ability of the skilled artisan to reproduce the claimed antibody, that concern is more one of enablement than written description.

CONCLUSIONS OF LAW

We find that the description of the antigen used to produce the claimed antibody, *i.e.*, the PR B Form 412-562 antigen, which was recombinantly produced, is sufficient to meet the written description requirement of 35 U.S.C. § 112, first paragraph, of the claims to the antibody.

The rejection of claims 21-27, 29, and 30 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, is therefore reversed.

ISSUE (Enablement)

The Examiner concludes that claims 21-27, 29, and 30 do not meet the enablement requirement of 35 U.S.C. § 112, first paragraph.

Appellants contend that the Specification provides thorough teachings and working exemplifications describing how to make and use the claimed monoclonal antibody and claimed selection methods.

Thus, the issue on Appeal is: Are the teachings and working exemplifications in the Specification describing how to make and use the claimed monoclonal antibody and claimed selection methods sufficient to enable the claimed antibodies and methods?

FINDINGS OF FACT

FF15 The Examiner rejects claims 21-27, 29, and 30 under 35 U.S.C. § 112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, particularly the invention commensurate in scope with these claims." (Ans. 7.)

FF16 The Examiner made the following findings with respect to the factors set out in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). [1]

FF17 *The Direction and Guidance provided by Appellants/Working Examplest*: The Examiner finds that the only guidance provided by the Specification is "a single species of antibody of unknown structure and properties which functions as intended by appellant." (Ans. 7.)

FF18 *State of the Art/The level of Skill in the Art and Lack of Predictibility*: The Examiner notes that the Specification teaches methods of screening antibodies, but finds that "the reproducibility of making another antibody of similar characteristics to the SP2 antibody is not known and is entirely unpredictable." (*Id.* at 7.) The Examiner relies on Press, finding that it teaches that

> after conventional immunization with N-terminally truncated A isoform of the human progesterone receptor (PR), which

---

[1] The factual considerations discussed in *Wands* are: (1) the quantity of experimentation necessary to practice the invention, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

> comprises the same sequence used by appellant and which is even less similar (about 63 mismatches) in sequence to the corresponding sequence in the protein found in the mouse, **none** of the isolated murine anti-PR monoclonal antibodies performed in the screening method as functional for PR detection without antigen retrieval in formalin-fixed and paraffin embedded tissue sections after deparaffinization and rehydration (see page 810).

(Ans. 8.) Thus, according to the Examiner, Press supports that it is unpredictable whether generation of antibodies having the characteristics of the SP2 antibody could be reproduced (*id.*). The Examiner notes further that in Press, it was only after immunization with a formalin fixed PR a isoform that two antibodies were elicited that allowed for PR detection without initial antigen retrieval (*id.*).

FF19 *Undue Experimentation*: The Examiner finds that the amount of experimentation required to determine functional structures or modifications for usable antibodies other than the SP2 antibodies would be undue (*id.* at 7).

FF20 The Examiner also objects to the Specification, and rejected claims 21-27, 29, and 30 under 35 U.S.C. § 112, first paragraph, "as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the disclosed biological materials (which may be enabled) are: (1) known and readily available to the public; (2) reproducible from the written description; or, (3) deposited in compliance with the criteria set forth in 37 C.F.R. §§ 1.801-1.809." (Ans. 9.)

FF21 The Examiner concludes it would require an "undue experimentation to reproduce the monoclonal antibody species chemically as produced by the hybridoma designated SP2 and encompassed by the claims." (*Id.*)

FF22 The Examiner notes that a suitable deposit would satisfy the enablement requirement for the antibody species produced by the hybridoma (*id.*).

FF23 Press discloses two antibodies, PgR636 and PgR1294, that do not require antigen retrieval, *i.e.*, heat pretreatment, for the immunohistochemical detection of progesterone receptors in formalin fixed and paraffin embedded tissue samples (Press Abstract).

FF24 The antibodies were prepared using formalin treated, full-length PR-A as the antigen (*id.* at 800, second column-801, first column).

FF25 Press teaches that in "parallel experiments, we used unfixed PR as antigen and screened hybridomas for IHC [immunohistochemical] detection of PR in formalin-fixed paraffin tissue sections. None of the Mabs isolated from these other cell fusions was able to specifically stain for PR in the absence of antigen retrieval." (*Id.* at 810, first column.)

FF26 Thus, Press appears to teach that full length, unfixed PR A was used as the antigen in the parallel experiments (FF25), and not N-terminally truncated A isoform of the human progesterone receptor, as found by the Examiner (FF18).

PRINCIPLES OF LAW

"When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation

as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." *In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993).

"[T]o be enabling, the specification . . . must teach those skilled in the art how to make and use *the full scope of the claimed invention* without 'undue experimentation.'" *Wright*, 999 F.2d at 1561, (emphasis added), *quoted in Genentech, Inc. v. Novo Nordisk, A/S,* 108 F.3d 1361, 1365, (Fed. Cir. 1997). Thus, "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 & n. 23, (Fed. Cir. 1991), *quoted in Enzo Biochem, Inc. v. Calgene, Inc.,* 188 F.3d 1362, 1374, (Fed. Cir. 1999). Moreover, the test of whether the experimentation required is undue "is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine." *Wands*, 858 F.2d at 737.

ANALYSIS

Appellants argue that the Specification "provides thorough teachings and working exemplification describing how to make and use the claimed monoclonal antibody and claimed selection method." (App. Br. 6.)

We find that Appellants have the better argument. The Specification teaches the immunogen used to make the claimed antibody (FF5), and further teaches that two clones were obtained, of which the SP2 clone produced the antibody with the strongest staining (FF6). Thus, given the

guidance provided in the Specification, while it may require a considerable amount of routine experimentation to obtain additional rabbit monoclonal antibodies having the claimed characteristics, such experimentation would not be undue.

We have considered the Press reference, but contrary to the finding of the Examiner that none of the isolated murine anti-PR monoclonal antibodies performed in the screening method as functional for PR detection without antigen retrieval in formalin-fixed and paraffin embedded tissue sections (FF18), it appears that the immunogen used was actually the full length PR A receptor (FF25, FF26). Thus, Press does not support the Examiner's conclusion that it would be unpredictable to produce antibodies having the claimed characteristics using the immunogen taught by the Specification, *i.e.*, recombinantly produced PR B 412-562 antigen.

Moreover, because we conclude that the Examiner has not established that one could not reproduce the claimed antibody, and as none of the claims on appeal specifically require the rabbit monoclonal antibody produced by clone SP2, we also conclude that Appellants need not deposit the SP2 antibody to satisfy the enablement requirement.

CONCLUSIONS OF LAW

Thus, we conclude that the teachings and working exemplifications in the Specification describing how to make and use the claimed monoclonal antibody and claimed selection methods are sufficient to enable the claimed antibodies and methods.

We thus reverse the rejection of claims 21-27, 29, and 30 under 35 U.S.C. § 112, first paragraph, as not meeting the enablement requirement; and also reverse the rejection of claims 21-27, 29, and 30 under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the disclosed biological material (which may be enabled) are: (1) known and readily available to the public; (2) reproducible from the written description; or, (3) deposited in compliance with the criteria set forth in 37 C.F.R. §§ 1.801-1.809.

REVERSED

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dm

Ex parte Gleave, 84 USPQ2D 1681 (Bd. Pat. App. & Int. 2006)

Ex parte Gleave
Bd. Pat. App. & Int. BdPatApp&Int
U.S. Patent and Trademark Office Board of Patent Appeals and Interferences
84 USPQ2D 1681
Appeal No. 2005-2447

Decided January 31, 2006
1/31/2006

(Nonprecedential)

Headnotes

PATENTS

[1] Patentability/Validity — Anticipation — Identity of elements (§115.0704)

Finding that claim limitations not expressly found in prior art reference are nonetheless inherent in reference may give rise to anticipation, but inherency cannot be established by probabilities or possibilities; in present case, reference cited by patent examiner does not establish prima facie case of anticipation for claims directed to method of delaying progression of hormone-regulated mammalian tumor cells to androgen-independent state by treating cells with antisense oligonucleotide that inhibits expression by tumor cells of insulin-like growth factor binding protein known as "IGFBP-5," since cited reference, which describes effects of inhibition of IGFBP-5 expression in cancer cell line different from that used by applicants herein, teaches, at most, that such inhibition might delay progression to androgen independence, not that it will, and this is insufficient to establish inherency; however, anticipation rejection is affirmed as to composition claims, directed to "a composition for treatment of hormone-regulated cancer comprising an antisense oligonucleotide which inhibits expression of IGFBP-5 by hormone-regulated tumor cells," since applicants have not shown how IGFBP-5 antisense oligonucleotide composition, as described in prior art reference, would be unsuitable for administration to animal, or how it may be distinguished from claimed composition.

[2] Patentability/Validity — Obviousness — Combining references (§115.0905)

Prior art references cited by patent examiner do not establish prima facie case of obviousness for claims directed to methods of delaying progression of hormone-regulated tumor cells to androgen-independent state, to treating hormone-responsive cancer, and to delaying metastatic boney progression of tumors sensitive to insulin-like growth factor known as "IGF-1" by inhibiting expression of IGF binding protein known as "IGFBP-5," since, according to examiner, prior art teaches that prostatic tumor cells over-express IGFBP-5 and that IGFBP-5 is involved in tumorigenesis, and that it would therefore be obvious for person skilled in art to inhibit IGFBP-5 expression in prostatic tumor cells, but this interpretation of prior art teaching is overly expansive, in that results of experiments

described in prior art do not disclose or suggest all limitations of applicants' invention, and record does not provide evidence that those skilled in art would have had reasonable expectation of success.

[3] Patentability/Validity — Specification — Written description (§115.1103)

Patent examiner's rejection for lack of adequate written description is reversed as to claims requiring antisense oligonucleotides that inhibit expression of insulin-like growth factor binding protein, known as "IGFBP-5," in hormone-regulated mammalian tumor cells, even though specification describes only mouse and human IGFBP-5 sequences that could be targeted with antisense oligonucleotides, since actual reduction to practice is not necessary to satisfy written description requirement, since specification sets forth sequences of DNA molecules encoding mouse and human IGFBP-5s and several antisense sequences targeting specific regions of mouse and human IGFBP-5 DNAs, and since examiner has not explained why person skilled in art would not expect mouse and human DNAs to be representative of, or have considerable structural similarity to, IGFBP-5s in other mammals; however, rejection is affirmed as to claims directed to process for inhibiting expression of IGFBP-5 in hormone-responsive cells using "a composition effective to inhibit expression of IGFBP-5," since specification discloses only aforementioned antisense oligonucleotides, and thus provides no description of which compositions have functional property recited in claims, and definition by function alone is insufficient, in that it only indicates what composition does, rather than what it is.

[4] Patentability/Validity — Specification — Enablement (§115.1105)

Patent examiner's rejection for lack of enablement is reversed with respect to claims directed to antisense oligonucleotides used to inhibit expression by tumor cells of insulin-like growth factor binding protein known as "IGFBP-5," and to methods of treatment using antisense oligonucleotides, even though antisense therapy is highly unpredictable field, since applicants identified murine and human IGFBP-5s as appropriate targets in treating androgen-dependent cancers, and identified antisense IGFBP-5 molecules that can delay progression to androgen independence in recognized tumor model and/or inhibit expression of IGFBP-5 in human prostate cancer cell lines, since this concrete guidance weighs in favor of finding specification enabling for claims at issue, and since examiner has not explained why identifying other antisense IGFBP-5 molecules capable of achieving desired result would require undue experimentation, in view of specific guidance provided in applicants' working examples.

Case History and Disposition

Patent application of Martin Gleave and Hideaki Miyake (no. 09/619,908), claiming method for delaying progression of hormone-regulated tumor cells to hormone independence, therapeutic method for treatment of patients suffering from hormone-regulated cancers, and therapeutic agents effective for use in such methods. Applicants appeal from examiner's final rejection of claims. Affirmed in part and reversed in part.

[Editor's note: The Board of Patent Appeals and Interferences states that this opinion is not binding precedent of the board.]

Judge:

Before Scheiner, Adams, and Mills, administrative patent judges.

Opinion Text

Opinion By:

Scheiner, J.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the final rejection of claims

Page 1683

1-23 and 26-40. Claims 24 and 25, also pending in the application, have been allowed.

BACKGROUND

> Insulin-like growth factor (IGF)-I and IGF-II are potent mitogens for many normal and malignant cells. Accumulating evidence suggests that IGFs play an important role in the pathophysiology of prostatic disease and breast cancer... .
>
> The biological response to [IGFs] is regulated by various factors, including IGFBPs [(insulin-like growth factor binding proteins)]. To date, six IGFBPs have been identified whose function is believed to involve modulation of the biological actions of the IGFs through high affinity interactions... However, some evidence suggests biological activity for IGFBPs that are independent of IGFs, ... and both stimulatory and inhibitory effects of IGFBPs on cell proliferation have been reported under various experimental conditions... .
>
> Specification, pages 1-2.

"[P]rostate cancer is an androgen-sensitive tumor, [thus,] androgen withdrawal ... is utilized in some therapeutic regimens ... [and] leads to extensive apoptosis in the prostate tumor, and hence to a regression of the disease. However, ... apoptosis is not complete, and a progression of surviving tumor cells to androgen-independence ultimately occurs." *Id.,* page 1. The present invention is concerned with delaying the ultimate progression of tumor cells to androgen-independence.

Appellants "initially characterized the changes [in] IGFBPs expression in the Shionogi tumor model[1] after castration and during [progression to androgen-independence]" (Specification, page 5). "Of the IGFBPs expressed in Shionogi tumors, the most dramatic changes in expression were observed with IGFBP-5. Despite undetectable levels in [androgen-dependent] intact tumors, IGFBP-5 expression is highly upregulated after castration, and remains highly expressed in [androgen-independent] tumors." *Id.,* pages 5-6. Moreover, "[t]he pattern of IGFBP-5 upregulation in the Shionogi tumor model during [progression to androgen-independence] ... is similar to that in rat prostate ... and human prostate" (*id.,* page 6).

According to appellants, antisense oligodeoxynucleotides (ODNs) complementary to portions of the gene encoding IGFBP-5 "inhibit[ ] cell proliferation and induce[ ] cell cycle arrest in Shionogi tumor cells in a time- and dose-dependent manner ... [and do] not appear to

induce apoptosis either *in vitro* or *in vivo* ... suggest[ing] that antisense IGFBP-5 activity occurs via inhibition of cell proliferation rather than induction of apoptosis." *Id.* Appellants "hypothesized that targeting upregulation precipitated by androgen using [an] antisense strategy might inhibit progression to androgen-independence." *Id.,* page 7. In appellants' "*in vivo* experiments, administration of antisense IGFBP-5 after castration delayed time to [androgen-independence] ... and inhibited [androgen-independent] recurrent tumor growth." *Id.*

THE CLAIMS

The present invention is directed to "a method for delaying the progression of hormone-regulated (prostatic or breast) tumor cells to hormone (e.g. androgen or estrogen) independence, a therapeutic method for the treatment of individuals ... suffering from hormone regulated cancers, such as breast or prostate cancer, and therapeutic agents effective for use in such methods." Specification, page 4. In addition, the present invention is directed to a method of inhibiting or delaying metastatic boney progression of an IGF-1 sensitive tumor in a mammal. We note that the claims on appeal require an antisense oligonucleotide that inhibits expression of IGFBP-5, with the exception of method claims 8, 12, 15, 19, 39 and 40, which merely require "a composition effective to inhibit expression of IGFBP-5."

Claims 1, 8, 15 and 22 are representative of the subject matter on appeal:

1. A method for delaying progression of hormone-regulated mammalian tumor cells to an androgen-independent state, comprising treating hormone-sensitive mammalian tumor cells with an antisense oligonucleotide which inhibits expression of IGFBP-5 by the tumor cells.

8. A method for treating a hormone-responsive cancer in a mammalian individual suffering from hormone-responsive cancer, comprising the steps of initiating hormone-withdrawal to induce apoptotic cell death of hormone-responsive cancer cells in the individual, and administering to the individual a composition effective to inhibit expression of IGFBP-5 by the hormone-responsive cancer cells, thereby delaying the progression of hormone-responsive cancer cells to a hormone-independent state in the individual.

15. A method for inhibiting or delaying metastatic boney progression of an IGF-1 sensitive tumor in a mammal, comprising the step of administering to the mammal a composition effective to inhibit expression of IGFBP-5 by the hormone-responsive cancer cells, thereby inhibiting or delaying metastatic boney progression of the tumor.

22. A composition for treatment of hormone-regulated cancer comprising an antisense oligonucleotide which inhibits expression of IGFBP-5 by hormone-regulated tumor cells.

THE REJECTIONS

The claims stand rejected as follows:

I. Claims 1, 5, 22 and 36-38[2] under 35 U.S.C. §102(b) as anticipated by Huynh.[3]

II. Claims 1-3, 5, 6, 22, 23, 26-28, and 36-38[4] under 35 U.S.C. §103(a) as unpatentable over Huynh in view of Kiefer,[5] Baracchini[6] and Nickerson.[7]

III. Claims 1-3, 4, 6, 8-10, 12, 13, 15-17, 19, 20, 22, 23 and 38-40 under the first paragraph of 35 U.S.C. §112, written description.

IV. Claims 1-23 and 26-40 under the first paragraph of 35 U.S.C. §112, enablement.

DISCUSSION

I. Anticipation

Claims 1, 5, 22 and 36-38 stand rejected under 35 U.S.C. §102(b) as anticipated by Huynh. Claims 1, 5 and 38 are method claims, while claims 22, 36 and 37 are composition claims. Appellants argue that the method and composition claims do not stand or fall together because "anticipation of a method claim requires a different content of the reference than a composition claim, which need only disclose the same composition, rather than the same method steps." Brief, page 3. Accordingly, we will consider claim 1 to be representative of the method claims, and claim 22 to be representative of the composition claims—claims 5 and 38 will stand or fall with claim 1, while claims 36 and 37 will stand or fall with claim 22.

Claim 1 is directed to a method of delaying progression of hormone-regulated mammalian tumor cells to an androgen-independent state by treating the cells with an antisense oligonucleotide which inhibits expression of IGFBP-5 by the tumor cells. According to the examiner, "a key limitation is that the method steps are carried out in hormone sensitive mammalian tumor cells" (Answer, page 14), and "Huynh discloses administering" an antisense oligomer comprising 21 nucleotides targeted to IGFBP-5 to breast cancer cells" (*id.,* page 5). The examiner acknowledges that Huynh says nothing about delaying progression of hormone-regulated mammalian tumor cells to an androgen-independent state, but argues that "any recited outcome such as that is merely considered to be an inherent feature,

since all the structural and manipulative features of the claim are present in Huynh" (*id.*).

[1] It is well settled that a prior art reference may anticipate even when claim limitations are not expressly found in that reference, but are nonetheless inherent in it. *See,* e.g., *Atlas Powder Co. v. IRECO Inc.,* 190 F.3d 1342, 51 USPQ2d 1943 (Fed. Cir. 1999); *Titanium Metals Corp. v. Banner,* 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985). However, it is also the case that "[i]nherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *In re Oelrich,* 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

Here, Huynh teaches that "IGFBP-5 can either stimulate or inhibit cellular proliferation in different experimental systems ... suggest[ing] that there are poorly characterized complexities in IGFBP-5 action" (Huynh, pages 1503-1504). Indeed, on this record, there is no dispute that "Huynh [ ] actually teach[es] that antisense to IGFBP-5 stimulates cell proliferation in the [MCF-7] breast cancer cell line used" (Answer, page 14), while it inhibits proliferation in the Shionogi tumor cells used by appellants. According to the examiner, this variation in the effects of antisense IGFBP-5 is irrelevant "because cellular proliferation (or inhibition thereof) is not recited as a claim limitation" (*id.*). In our view, however, this variation is relevant because it shows that in the only directly comparable parameter of record, the two cell lines react differently to inhibition of IGFBP-5. While Huynh says nothing about delayed progression to androgen-independence, it is not unreasonable to expect that the two cell lines might react differently to inhibition of IGFBP-5 in this respect as well,

especially in light of Huynh's suggestion that the actions of IGFBP-5 are poorly characterized. In our view, the examiner has established that inhibition of IGFBP-5 in Huynh's MCF-7 cells *might* delay progression to androgen-independence, but has not established that it *will.* As discussed above, this is not sufficient to establish a *prima facie* case of anticipation based on inherency.

Accordingly, the rejection of claims 1, 5 and 38 as anticipated by Huynh is reversed.

Claim 22, however, stands on a different footing. Claim 22 is directed to "a composition for treatment of hormone-regulated cancer comprising an antisense oligonucleotide which inhibits expression of IGFBP-5 by hormone-regulated tumor cells." Huynh plainly describes an IGFBP-5 antisense oligodeoxynucleotide which reduces expression of IGFBP-5 in human breast cancer cells. Appellants argue that "the phrase 'for treatment of hormone-regulated cancer' is more than a statement of intended use and deserves to be given weight in assessing the scope of the claims." Brief, page 7. According to appellants, "Huynh's antisense is not used in the treatment of any animal or human ... [thus,] [t]here is no teaching of a composition suitable for administration in the treatment of cancer." *Id.* Nevertheless, appellants have not pointed out anything which makes Huynh's IGFBP-5 antisense oligonucleotide composition unsuitable for administration to an animal, or which distinguishes it from the claimed IGFBP-5 antisense oligonucleotide composition in any way.

Accordingly, the rejection of claim 22 as anticipated by Huynh is affirmed. As discussed above, claims 36 and 37 stand or fall with claim 22, thus the rejection of claims 36 and 37 as anticipated by Huynh is affirmed as well.

II. Obviousness

Claims 1-3, 5, 6, 22, 23, 26-28, and 36-38 stand rejected under 35 U.S.C. §103(a) as unpatentable over Huynh in view of Kiefer, Baracchini and Nickerson. Having already determined that Huynh anticipates the subject matter of claims 22, 36 and 37, we affirm the rejection under 35 U.S.C. §103(a) with respect to those claims. "[A]nticipation is the epitome of obviousness." *Connell v. Sears, Roebuck & Co.,* 722 F.2d 1542, 1548, 220 USPQ 193, 198 (Fed. Cir. 1983).

Claims 1-3, 5, 6, 23, 26-28 and 38, on the other hand, are directed to methods of delaying the progression of hormone-regulated tumor cells to an androgen-independent state; to treating a hormone-responsive cancer; and to delaying metastatic boney progression of IGF-1 sensitive tumors by inhibiting IGFBP-5.

The examiner relies on Huynh for disclosure of "an antisense oligomer comprising 21 nucleotides targeted to IGFBP-5 that was administered to breast cancer cells" (Answer, page 6); on Kiefer for disclosure of the translation initiation and termination regions of IGFBP-5 (*id.*); and on Baracchini for "teach[ing] that the translation initiation and termination regions are preferred regions for targeting with antisense oligos" (*id.*). According to the examiner, these references provide motivation for targeting particular regions of

IGFBP-5 in order to inhibit its effects. *Id.,* pages 6-7.

Nevertheless, in our view, the dispositive issue here is the examiner's proposed rationale for inhibiting IGFBP-5 in tumor cells in the first place. The underlying premise of the examiner's rejection is that "Nickerson teaches that prostatic tumor cells over-express IGFBP-5 and [that IGFBP-5] is involved in tumorigenesis" (*id.,* page 6), and that, therefore, it would have

been obvious for one skilled in the art to inhibit IGFBP-5 expression in prostatic tumor cells (*id.*, page 7).

[2] We see no factual basis for the examiner's expansive interpretation of Nickerson's teachings. Nickerson's experiments were designed "to study the gene expression of IGFBPs during involution of the rat ventral prostate after castration." Nickerson, page 807. The experiments demonstrated that "IGFBP-5 mRNA increases in the ventral prostate 2-fold by 24 h and 5-fold by 72 h [ ] in keeping with the hypothesis that IGFBP-5 may be involved in apoptosis resulting from steroid hormone deprivation." *Id.,* page 809, left-hand column. According to Nickerson, the experimental system could not determine "whether IGFBPs cause apoptosis in the ventral prostate or are upregulated as a result of apoptosis." *Id.,* right-hand column. Either way, the examiner has not explained how Nickerson's observations suggest that IGFBP-5 is involved in tumorigenesis, or why one skilled in the art would have wanted to inhibit its effects.

The examiner bears the initial burden of establishing *prima facie* obviousness. *See In re Rijckaert,* 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). To support a *prima facie* conclusion of obviousness, the prior art must disclose or suggest all the limitations of the claimed invention. *See In re Lowry,* 32 F.3d 1579, 1582, 32 USPQ2d 1031, 1034 (Fed. Cir. 1994). In addition, the record must provide evidence that those of skill in the art would have had a reasonable expectation of success in doing so. *See In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

We agree with appellants that the examiner's rejection "fails to state a *prima facie* case of obviousness." Brief, page 8. The rejection of claims 1-3, 5, 6, 23, 26-28 and 38 under 35 U.S.C. §103 is reversed.

III. Written Description

Claims 1-3, 4, 6, 8-10, 12, 13, 15-17, 19, 20, 22, 23 and 38-40 stand rejected under the first paragraph of 35 U.S.C. §112, as lacking adequate written descriptive support.

"The 'written description' requirement serves a teaching function, ... in which the public is given 'meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time.'" *University of Rochester v. G.D. Searle & Co., Inc.,* 358 F.3d 916, 922, 69 USPQ2d 1886, 1891 (Fed. Cir. 2004) (citation omitted). Another "purpose of the 'written description' requirement is ... [to] convey with reasonable clarity to those skilled in the art that, as of the filing date [ ], [the applicant] was in possession of the invention." *Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). *See also Enzo Biochem Inc. v. Gen-Probe Inc.,* 296 F.3d 1316, 1329, 63 USPQ2d 1609, 1617 (Fed. Cir. 2002). The requirement is satisfied when the specification "set[s] forth enough detail to allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed." *University of Rochester,* 358 F.3d at 928, 69 USPQ2d at 1896. Whether or not a specification satisfies the requirement is a question of fact, which must be resolved on a case-by-case basis (*Vas-Cath*, 935 F.2d at 1562-63, 19 USPQ2d at 1116), and it is the examiner's "initial burden [to] present[ ] evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims" (*In re Wertheim,* 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976)).

[3] With respect to claims 1-3, 4, 6, 9, 10, 13, 16, 17, 20, 22, 23 and 38, we disagree with the examiner's rationale and conclusion. These claims require antisense oligonucleotides, of

varying scope, which inhibit expression of IGFBP-5 in hormone-regulated mammalian tumor cells. The examiner argues that "[t]he specification ... only describes two target IGFBP-5 sequences, [mouse and human] ... , and does not describe any additional sequences that can be targeted via antisense oligos. Without such a description, the skilled artisan would not be able to envision any other target sequences and thus would not be able to synthesize an antisense oligo specific for the sequence" (Answer, page 8), and moreover, would be "required to undertake de novo experimentation to isolate and identify IGFBP-5 encoding nucleic acids" (*id.*).

Nevertheless, "applicants have some flexibility in the 'mode selected for compliance'

with the written description requirement" (*University of Rochester,* 358 F.3d at 928, 69 USPQ2d at 1896), and it is well settled that actual reduction to practice is not necessary to satisfy the requirement (*id.* at 926, 69 USPQ2d at 1894). On the other hand, "[i]n claims to genetic material ... [a] definition by function ... does not suffice to define [a] genus because it is only an indication of what the [material] does, rather than what it is." *University of California v. Eli Lilly and Co.,* 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The court explained that "[a]n adequate written description of a DNA ... 'requires a precise definition, such as by structure, formula, chemical name, or physical properties,'" (*id.* at 1566, 43 USPQ2d at 1404) while "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus" (*id.* at 1568, 43 USPQ2d at 1406). Subsequently, the court clarified that "the written description requirement would be met for [a claim] ... if [a] functional characteristic ... were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed." *Enzo Biochem,* 296 F.3d at 1324-25, 63 USPQ2d at 1613.

Here, the specification sets forth the sequences of DNA molecules encoding the mouse and human IGFBP-5s, as well as a number of antisense sequences targeting specific regions of the mouse and human IGFBP-5 DNAs. The examiner's rationale would seem to limit the claimed genus to only those antisense oligonucleotides explicitly recited, without explaining why one skilled in the art would not have expected the mouse and human DNAs to be representative of, or have considerable structural similarity to, DNA encoding IGFBP-5 in other mammals. Again, it is the examiner's "initial burden [to] present[ ] evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims" (*Wertheim,* 541 F.2d at 263, 191 USPQ at 97). We find that the examiner has not done so.

Accordingly, the rejection of claims 1-3, 4, 6, 9, 10, 13, 16, 17, 20, 22, 23 and 38 as lacking adequate written descriptive support under 35 U.S.C. §112, first paragraph, is reversed.

With respect to claims 8, 12, 15, 19, 39 and 40, however, we agree with the examiner that adequate written descriptive support is lacking. We note that these claims merely require "a composition" effective to inhibit expression of IGFBP-5. The only such compositions disclosed in the specification are the aforementioned antisense oligonucleotides. The examiner's position is essentially that the specification does not provide "any description, structural[ ] or otherwise, of IGFBP-5 inhibitors other than the instantly described antisense

oligo[nucleotides]" and that the instantly described antisense oligonucleotides are "not representative of the breadth of inhibitors sought in the instant claims" (Answer, page 8).

Appellants argue that "the invention is based on the discovery ... that reducing the expression of IGFBP-5 in hormone-responsive cancer cells has therapeutic benefits" (Brief, page 12), and "antisense inhibitors of IGFBP-5 expression [are] examples of a methodology that can be used in practicing the methods." (*id.,* page 13). Appellants argue that the invention "is not antisense technology *per se*. It is also not the identification of IGFBP-5, nor any and all inhibitors of IGFBP-5 expression" (*id.,* page 12).

These arguments are not persuasive. The Federal Circuit has recently held that the written description standard discussed in *Eli Lilly* applies to methods as well as products. *See University of Rochester v. G.D. Searle & Co., Inc.,* 358 F.3d 916, 926, 69 USPQ2d 1886, 1894 (Fed. Cir. 2004): "Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods."

The facts in *Rochester* are similar to those of the instant application. *Rochester* involved a "method for selectively inhibiting PGHS-2 activity in a human host, comprising administering *a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product* to a human host in need of such treatment." *Id.* at 920, 69 USPQ2d at 1888 (emphasis added). The court noted that the relevant patent described the cells needed to screen for compounds having the recited property, as well as "assays for screening compounds, including peptides, polynucleotides, and small organic molecules to identify those

that inhibit the expression or activity of the PGHS-2 gene product." *Id.* At 927, 69 USPQ2d at 1895. Nevertheless, the court concluded that the patent's disclosure was inadequate to enable the claimed method because the patent "[did] not disclose just *which* peptides, polynucleotides, and small organic molecules have the desired characteristic of selectively inhibiting PGHS-2." *Id.* (emphasis in original, internal quotations omitted). "Without such disclosure, the claimed methods cannot be said to have been described." *Id.*

In this case, as in *Rochester,* the claims are directed to a process for accomplishing a desired result (in *Rochester,* selectively inhibiting PGHS-2 activity in a human host; here, "inhibiting expression of IGFBP-5 in hormone-responsive cells") using a composition having a specified functional property (in *Rochester,* a "non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product"; here, "a composition effective to inhibit expression of IGFBP-5"). And in this case, as in *Rochester,* the specification provides no description whatsoever of just *which* compositions have the functional property recited in the claims—the genus recited in the claims is defined exclusively in functional terms, i.e., in terms of what the members of the genus *do,* rather than what they *are.*

As discussed above, "[a] definition by function ... does not suffice to define [a] genus because it is only an indication of what the [material] does, rather than what it is." *Eli Lilly,* 119 F.3d at 1568, 43 USPQ2d at 1406. To paraphrase *Eli Lilly,* naming a type of material, which may or may not exist, in the absence of knowledge as to what that material consists of, is not a description of that material. *See id.* Accordingly, the rejection of claims 8, 12, 15, 19, 39 and 40 as lacking adequate written descriptive support under 35 U.S.C. §112, first paragraph, is affirmed.

IV. Enablement

Claims 1-23 and 26-40, all the claims on appeal, stand rejected under 35 U.S.C. §112, first paragraph, as lacking enablement. According to the examiner, the claims are drawn to "antisense oligo[nucleotides] targeted to any transcript of IGFBP-5 as well as methods of treatment using said antisense oligo[nucleotides]" (Answer, page 9), but the specification "is only enabling for antisense oligos of SEQ ID NO:1 targeted to the IGFBP-5 transcripts of [murine] SEQ ID NO:13, and for the use of SEQ ID NOS: 2, 3 and 9 in the inhibition of SEQ ID NO:14 *in vitro*, and does not provide guidance on the *in vivo* inhibition of [human] SEQ ID NO:14" (*id.*).

With respect to claims 1-7, 9-11, 13, 14, 16-18, 20-23 and 26-48, all of which require an antisense oligonucleotide capable of inhibiting expression of IGFBP-5, we do not agree with the examiner's rationale or conclusion, for the reasons that follow. Initially, however, we note that the examiner has focused exclusively on the therapeutic use of antisense oligonucleotides, and has not separately addressed the enablement of those claims that do not require antisense oligonucleotides (as was done in the written description rejection above). Nevertheless, our affirmance of the written description rejection for claims 8, 12, 15, 19, 39 and 40 constitutes a disposition of these broader claims, so we need not reach the merits of the enablement rejection with respect to these claims.

Returning to claims 1-7, 9-11, 13, 14, 16-18, 20-23 and 26-48, then, we find that the reasons cited in support of the examiner's rejection are insufficient to support the examiner's conclusion that these claims are not enabled by the specification.

"The first paragraph of 35 U.S.C. §112 requires, *inter alia,* that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.' *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).[8] That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation is 'undue.'" *In re Vaeck,* 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (emphasis in original). Nevertheless, "[w]hen rejecting a claim under the enablement requirement of section 112," it is well settled

that "the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

According to the examiner, "the clinical application of antisense therapy is a highly unpredictable art due to obstacles that still face antisense therapy" (Answer, page 9). The obstacles enumerated by the examiner are essentially: the identification of an appropriate target in the disease process; the identification of a molecule that can interfere with the disease process through specific recognition and affinity; the complexity of cellular uptake of oligonucleotides; and physical barriers due to internal structures of target RNAs and associations with cellular proteins. *Id.,* pages 9-10. In addition, the examiner relies on Gewirtz[9] and Branch[10] as evidence that "'the antisense approach has generated controversy [among those of skill in the art] with regard to mechanism of action, reliability,

and ultimate therapeutic utility'" (*id.,* page 10), and the sense in the art is that "'efforts should be increased ... to learn how they may be used successfully in the clinic'" (*id.*).

[4] We have no reason to doubt the examiner's assessment of the state of the art in general, and we think it is fair to say that the field of antisense therapy is indeed recognized as highly unpredictable by those of skill in the art. Nevertheless, appellants point out, and the examiner appears to acknowledge, that appellants have identified the murine and human IGFBP-5s as appropriate targets in treating androgen-dependent cancers like prostate cancer and breast cancer, and that appellants have identified antisense IGFBP-5 molecules that can delay progression to androgen independence in the Shionogi tumor model (asserted to be a useful model of human prostate cancer) and/or inhibit expression of IGFBP-5 in human prostate cancer cell lines. See page 17 of the substitute Brief for Appellant (submitted June 10, 2004), and page 9 of the Answer. This concrete guidance, in the form of working examples, would seem to address a number of the examiner's specific concerns, and weigh in favor of finding the specification enabling for claims directed to antisense inhibition of IGFBP-5. In any case, the examiner has not explained why the specific guidance in the specification would not, at least to some extent, mitigate or counterbalance any remaining factors (e.g., the generally unpredictable nature of the field) tending to weigh against a finding of enablement. In other words, the examiner has not explained why identifying other antisense IGFBP-5 molecules capable of delaying progression of hormone-regulated tumor cells to androgen-independence, either *in vivo* or *in vitro* would have required undue experimentation, given the specific guidance provided by appellants in their working examples.

Accordingly, the rejection of claims 1-7, 9-11, 13, 14, 16-18, 20-23 and 26-48 as lacking enablement under the first paragraph of 35 U.S.C. §112 is reversed.

SUMMARY

I. The rejection of the claims under 35 U.S.C. §102(b) as anticipated by Huynh is affirmed with respect to claims 22, 36 and 37, and reversed with respect to claims 1, 5 and 38.

II. The rejection of the claims under 35 U.S.C. §103(a) as unpatentable over Huynh, Kiefer, Baracchini and Nickerson is affirmed with respect to claims 22, 36 and 37, and reversed with respect to claims 1-3, 5, 6, 23, 26-28 and 38.

III. The rejection of the claims under 35 U.S.C. §112, first paragraph, as lacking adequate written descriptive support is affirmed with respect to claims 8, 12, 15, 19, 39 and 40, and reversed with respect to claims 1-3, 4, 6, 9, 10, 13, 16, 17, 20, 22, 23 and 38.

IV. The rejection of the claims under 35 U.S.C. §112, first paragraph, as lacking enablement is reversed with respect to claims 1-7, 9-11, 13, 14, 16-18, 20-23 and 26-48. We do not reach the merits of this rejection with respect to claims 8, 12, 15, 19, 39 and 40.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR §1.136(a).

AFFIRMED-IN-PART

Footnotes

1 "The Shionogi tumor model is a xenograft of an androgen-dependent mouse mammary carcinoma that grows subcutaneously in male syngenic hosts." Specification, pages 4-5. Shionogi tumor cells "are highly tumorigenic and locally invasive ... [and] have been shown to respond to androgen withdrawal in a manner which mimics the observed behavior of prostatic tumor cells," that is, "androgen withdrawal precipitates apoptosis and tumor regression in a highly reproducible manner" (*id.,* page 5). "Further, changes in expression of peptides ... in human prostate cancer following castration and during progression to androgen-independence are similar to those observed in Shionogi tumor cells. Because of these similarities, the Shionogi tumor model mimics human prostate cancer and provides a very useful model for the evaluation of the ability of compounds to delay the onset of androgen-independence. Despite complete tumor regression after castration, rapidly growing androgen-independent Shionogi tumors invariably recur after one month, which provides a reliable end point to evaluate agents which can delay the progression to androgen-independence." *Id.*

2 Claims 36-38 were subject to this ground of rejection in the final rejection (paper no. 14, January 24, 2003), but were omitted from the examiner's statement of the rejection in the Answer. The omission of these claims appears to have been a typographical error, as they are specifically discussed in the examiner's response to appellants' arguments (see, e.g., page 16 of the Answer).

3 Huynh et al., "A Role for Insulin-like Growth Factor Binding Protein 5 in the Antiproliferative Action of the Antiestrogen ICI 182780," *Cell Growth & Differentiation,* Vol. 7, pp. 1501-1506 (November 1996)

4 Claim 40 was included in this rejection in the final rejection, but the rejection was withdrawn with respect to claim 40 in the Examiner's Answer (page 17).

5 Kiefer et al., "Molecular Cloning of a New Human Insulin-like Growth Factor Binding Protein," *Biochem. Biophys. Res. Commun.,* Vol. 176, No. 1, pp. 219-225 (1991).

6 U.S. Patent No. 5,801,154, issued to Baracchini et al. on September 1, 1998.

7 Nickerson et al., "Castration-Induced Apoptosis in the Rat Ventral Prostate is Associated with Increased Expression of Genes Encoding Insulin-Like Growth Factor Binding Proteins 2, 3, 4 and 5," *Endocrinology,* Vol. 139, No. 2, pp. 807-810 (1998).

8

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (BdPatApplnt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims (footnote omitted).

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

9 Giwirtz et al., "Facilitating Oligonucleotide Delivery: Helping Antisense Deliver on Its Promise," *Proc. Natl. Acad. Sci. USA,* Vol. 93, pp. 3161-3163 (April, 1996).

10 Branch, A.D., "A Good Antisense Molecule is Hard to Find," *TIBS,* Vol. 23, pp. 50 (February, 1998).

- End of Case -
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